

Combination Therapy of Lucentis (Ranibizumab) plus laser induced chorioretinal venous anastomosis for central retinal vein occlusion.

L-CVBS Study

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Protocol synopsis

Title of study: Combination Therapy of Lucentis (Ranibizumab) plus laser induced chorioretinal venous anastomosis for central retinal vein occlusion.

Objectives:

Primary Objective: To compare and establish whether there is a significant difference in the number of Lucentis injections according to the PRN retreatment protocol in the observational period from twelve to twenty four months in patients with visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) treated with either Lucentis/laser induced chorioretinal venous anastomosis (L-CRA) or Lucentis/sham L-CRA.

Secondary Objectives:

- 1) Mean average best corrected visual acuity (BCVA) change from baseline to Months 6, 12 and 24 between the L-CRA and Sham L-CRA treatment groups.
- 2) Residual central foveal thickness of macular measured by Spectral-domain OCT at Months 6, 12 and 24 for the two treatment groups.
- 3) Degree of peripheral retinal ischaemia between the two treatment groups as measured by Optus wide angle camera at Months 12 and 24.
- 4) Stability of both treatment groups in 2 year extension phase measured by BCVA, OCT and number of injections
- 5) Determine the nature and sequence of changes to radial peripapillary capillaries and deep capillary networks.

Methodology: Eyes with visual impairment due to macular oedema involving the centre of the fovea due to CRVO with a duration of less than 9 months prior to the baseline visit will be randomised 1:1 into Lucentis alone or L-CRA plus Lucentis groups.

Best-corrected visual acuity (BCVA) will be measured on a ETDRS lighthouse 4 meter chart.

Optical coherence tomography (OCT) will be used to measure centre point foveal thickness.

Fluorescein angiography (FA) will be used to measure retinal ischaemia.

OCTA will be used to examine the changes to the radial peripapillary and deep capillary networks.

Number of centers & patients: 58 patients from Lions Eye Institute Perth

Population: Eyes with central visual reduction due to perfused macular oedema secondary to central retinal vein occlusion.

Investigational drug: Intravitreal drug Lucentis (Ranibizumab 0.5 mg) in combination with Laser induced Chorioretinal venous anastomosis (L-CRA)

Reference therapy: Intravitreal injection of Lucentis alone as per CRUISE study.

Study duration: 24 months from baseline with additional 2 year extension

Objectives: Reduction in the number of Lucentis injections in the second year of the study in the combination group reflecting the fact that this treatment addresses all of the components causing macular oedema in CRVO unlike the Lucentis alone therapy.

Evaluation schedule:

Year 1.														
Month (\pm 3 days)														
	Baseline	0	1	2	3	4	5	6	7	8	9	10	11	12
Ophthalmic Exam	x		x	x	x	x	x	x	x	x	x	x	x	x
Informed consent	x													
Randomisation + LCRA or sham		x												
Injection			x	x	x	x	x	x	(x)	(x)	(x)	(x)	(x)	(x)
Telephone Check			x	x	x	x	x	x	(x)	(x)	(x)	(x)	(x)	(x)
ETDRS visual acuity	x	x	x	x	x	x	x	x	x	x	x	x	x	x
OCT	x		x	x	x	x	x	x	x	x	x	x	x	x
FA & Colour Photos	x							x						x

Year 2.													
Month (\pm 3 days)													
		13	14	15	16	17	18	19	20	21	22	23	24
Ophthalmic Exam		x	x	x	x	x	x	x	x	x	x	x	x
Injection		(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Telephone Check		(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
ETDRS visual acuity		x	x	x	x	x	x	x	x	x	x	x	x
OCT		x	x	x	x	x	x	x	x	x	x	x	x
FA & Colour Photos							x						x

	Years 3 and 4.											
	Month (\pm 7 days)											
	26*	28*	30*	32*	34*	36*	38*	40*	42*	44*	46*	48
Ophthalmic Exam	x	x	x	x	x	x	x	x	x	x	x	x
Injection	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	x
Telephone Check	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	
ETDRS visual acuity	x	x	x	x	x	x	x	x	x	x	x	x
OCT	x	x	x	x	x	x	x	x	x	x	x	x
FA & Colour Photos												x
OCTA + Additional OCT**												

*** = in years 3 and 4, the patient may miss a visit if the vision is stable and there is no macula oedema. A patient must be seen once every 4 months.**

**** - OCTA and additional OCT images will be performed once at any time point in years 3 and 4.**

(x) = injection only if required (as determined by V/A and OCT, see Section 3.1, Retreatment criteria for month seven to forty six).

(x) = telephone call only of injection occurred.

This study is registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN1261200004864.

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Ethics and Good Clinical Practice

This study will be performed according to the principles of Good Clinical Practice [Chapter 2 of the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP)], the declaration of Helsinki, and national laws and regulations about clinical studies. The study may not start without written Institutional Review Board/Independent Ethics Committee/Research Ethics Board approval and the written informed consent of the patient.

1. Introduction

Retinal vein occlusion are one of the commonest cause of severe vision loss after AMD and the second most common cause of retinal vascular blindness after diabetic retinopathy. The incidence of retinal vein occlusions increases with age and the Blue Mountains Eye Study has found an incidence of 0.7% in those younger than 60 years rising to almost 5% in those 80 years or older. Retinal vein occlusions are the second most frequent cause of unilateral blindness.

Retinal vein occlusions may be either branch or central and have different underlying causes but both have common effects on loss of central vision due to either macular ischaemia or perfused macular oedema. In this study those with visual loss due to macular ischaemia or hypo perfusion will be excluded and the study will consist of only those with vision loss due to perfused macular oedema due to CRVO.

The treatment of CRVO has largely been aimed at the sequelae of the venous obstruction. Laser photocoagulation has found to be effective in reducing the progression to neovascular

glaucoma in those ischaemic CRVO's with early iris neovascularisation. Various therapeutic agents have been injected into the vitreous to address macular oedema and these include agents such as Triamcinolone, Pegaptanib, Bevacizumab, and Ranibizumab. Both Bevacizumab and Ranibizumab have been reported in studies to show promising short term resolution of the macular oedema but repeated intravitreal injections are needed as the effects seem to typically last four to six weeks.

Macular oedema in central retinal vein occlusion is due to a combination of factors. The obstructed venous outflow increases the venous hydrostatic pressure and this is a significant contribution to macular oedema. Retinal hypoxia due to the slowing of blood transit through the retina causes upregulation of VEGF and other cytokines which affect the endothelial cell blood retinal barrier and enhance intraretinal leakage. The Cruise Trial has shown that repeated injections of Ranibizumab over a six month period can lead to a significant improvement in visual acuity compared to the natural history of this condition.

Whilst these intravitreal therapies are effective in the short term the effect of the other component of macular oedema i.e. the hydrostatic pressure elevation, in the long term is not known. To date there is only one study which has addressed the hydrostatic venous pressure elevation and this is The Central Vein Bypass Study where a high intensity laser is used to create an anastomosis between a retinal vein and a choroidal vein, as a means of bypassing the obstruction to venous outflow. This is the only study to date which has addressed causal pathology rather than simply addressing the sequelae of the retinal venous obstruction. While both treatments i.e. the laser induced chorioretinal venous anastomosis and the intravitreal anti-VEGF antibodies have shown improvements over the natural history of this condition, there may be a significant benefit in using their combined effects to achieve even faster and more long lasting visual gains. By addressing both causative components, visual acuity gains may be faster and more sustained without further therapy.

In the CVBS a high energy laser was required to create the necessary anastomotic connection between a retinal vein and a choroidal vein as a means of bypassing the obstruction to venous outflow in CRVO. The use of this laser will not in itself have any effect on the requirement for Lucentis in this study but is required to deliver the required anatomical defects in the Bruchs membrane and retinal vein as was determined in our earlier animal and experimental studies prior to commencing to use this technique in humans. This technique in the CVBS was associated with localized neovascularisation at the anastomosis site in 18.2% of patients which in most cases was minor however 9.1% of patients did undergo vitrectomy because of nonresolving vitreous haemorrhage or macular traction. The anti VEGF agent lucentis in this study will be used after the anastomosis has become established in the combination arm and will have the secondary advantage of reducing the likelihood of neovascular complications. The main role of the Lucentis will however be to address the VEGF mediated breakdown of the macular capillary endothelial barrier which is one causative component of the CRVO induced macular oedema. The other major component is the raised hydrostatic venous pressure which the anastomosis will address.

Significant points:

1. Central vein bypass study mean acuity gains for those with a successful anastomosis (76.4% in the CVBS study however 85% in the subset of this multicenter study who were treated in Perth) were not significantly different from the sham group until twelve months but there after remained stable without additional treatment out to eighteen months at the conclusion of follow up.

2. In the Cruise Trial, patients on average lost 7.2 letters of vision if the month six injection was missed with a corresponding increase in central retinal thickness, implying the causative factors in promoting the macular oedema are still active at this time.

3. In the Cruise Study, for the second six months, approximately 40% of patients in the previous treated group still required five or more injections of Lucentis, again implying that causative factors in macular oedema creation are still active.

4. A recent natural history study has indicated that the median time for resolution of macular oedema was 23-29 months from time of first diagnosis. (Hayreh et al, Ophthalmology 2011; 118:119-133)

5. The extension study to the CRUISE study (HORIZON trial Ophthalmology 2012;119:802-809) indicated that patients in the second year of Lucentis treatment for CRVO still required 3-3.5 injections and lost on average 4.5 letters of BCVA. Other longer term studies have indicated that oedema resolution does not occur in a percentage of patients with CRVO. The RETAIN study (Ophthalmology 2014;121:209-219) has indicated in a long term study (mean follow-up 49.7 months) only 44% of patients had oedema resolution after treatment with Lucentis and the remainder with residual oedema still requiring on average 5.9 injections in the 4th year. This does imply that whilst Lucentis is a very effective treatment for this condition in the short term there are components of the causative factors for the macular oedema that are not addressed by this therapy alone. The most likely cause for this is the elevated venous pressure that the L-CRA will address.

Rationale for the Combination approach of Lucentis plus L-CRA

Macular oedema in retinal vein occlusion is most likely due to the combined effects of raised intravascular pressure in the capillary bed secondary to the venous obstruction and hypoxia secondary to the reduced flow caused by reduced pressure differential across the arterial and venous circulations secondary to the increased venous exit resistance. The hypoxia will in turn up regulate factors such as VEGF. VEGF is known to be a potent inducer of vascular leakage and has been shown to be involved in and correlate with levels of intraretinal oedema in patients with diabetic macular leakage. VEGF antibodies e.g. Lucentis (Ranibizumab) have been shown in the Phase 3 clinical trial (CRUISE trial) to have a significant effect on macular oedema secondary to CRVO and to improve visual outcomes over what would be expected to occur in the natural history of this condition. This therapy only addresses one of the causative factors of the macular oedema and fails to address the elevation of the venous hydrostatic pressure. The Central Vein Bypass Trial (CVBS) addressed this component in a phase 3 trial and also showed a significant improvement in outcomes compared to what would be expected in the natural history.

This trial seeks to prove the hypothesis that a combination approach (bypass surgery plus Lucentis) will lessen the need for repeated Lucentis injections and also lead to a faster and more complete resolution of the macular oedema.

As both groups will receive intravitreal Lucentis on a prn basis after the initial 6 month mandatory monthly injection period, it is expected that the BCVA will remain the same between the 2 groups (with levels of improvement as per the CRUISE study). The anticipated difference will be the requirement for less injections in the combination group in the second year and, as the L-CRA becomes more haemodynamically significant, a more stable macular with less and less likelihood of developing recurrent oedema.

Both approaches have been proven to be beneficial compared to the natural progression of the condition with minimal side effects in multicenter randomized controlled clinical trials. Modification of this process may be achievable with an anti-VEGF agent delivered into the vitreous cavity. Lucentis (Ranibizumab) has also been shown to be a potent and effective inhibitor of neovascularisation in neovascular macular degeneration based on the Phase III clinical trials (MARINA and ANCHOR). The effectiveness of the delivery via intravitreal injection and its safety in the eye has been well demonstrated.

Rational for the 2 year extension study.

Recent studies have indicated that a significant number of patients have unresolved macular oedema requiring continued therapy with intravitreal Lucentis for up to and possibly longer than 4 years. In the extension study we aim to ensure that the patients in the control group still receive the best possible care according to current recommended standards. We also aim to show the longer term benefit of the L-CRA in lowering the venous pressure and not only reducing the number of intravitreal treatments required but also enabling them to be ceased altogether. Because of this we anticipate more stable long term vision in the combination treatment group.

2. Study Objectives

Primary Objective: To compare the number of Lucentis injections within the observational period from 12 to 24 months in patients with visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) treated with Lucentis/laser surgery (L-CRA) or Lucentis/sham laser surgery (L-CRA).

Secondary Objectives:

- 1) Mean average BCVA change from baseline compared to Months 6, 12 and 24 between the two treatment groups.
- 2) Mean change from baseline central foveal thickness (CFT) measured by Spectral-domain OCT at 6, 12 and 24 months.
- 3) Degree of peripheral retinal ischaemia between the two groups as measured by Optus wide angle camera at 12 and 24 months.

- 4) The 2 year extension will monitor the need for additional therapy in both treatment groups measured by BCVA and OCT changes.
- 5) Determine the nature and sequence of changes to radial peripapillary capillaries and deep capillary networks.

3. Investigational Plan

3.1. Overall study design

This phase IV randomised, comparative, blind trial will recruit treatment-naïve patients presenting with CRVO with visual reduction due to perfused macular oedema. At visit 1 (baseline), patients will be assessed for BCVA (using LogMAR chart) and retinal oedema (using OCT and FA). Fifty eight patients will be randomised 1:1 into one of two study groups: The first group will be treated with sham L-CRA followed with monthly standard intravitreal Ranibizumab 0.5 mg for 6 months as per the CRUISE study and thereafter monthly as needed per the retreatment criteria (prn). The second group will be treated with L-CRA followed by monthly intravitreal Ranibizumab 0.5mg as above for the first 6 months and then prn as per the retreatment criteria. The L-CRA will be performed at baseline and patients will be assessed with biomicroscopy at 5 weeks +/- 7 days following the laser attempt to determine patency of the L_CRA. Lucentis will then commence as per the protocol for 6 months and then prn as per the retreatment criteria. Patients will be monitored and OCT and ETDRS visual acuity will be performed monthly in the first two years and bimonthly in years 3 and 4. If visual acuity is stable and there is no macula oedema, visits may extend out to once every 4 months in years 3 and 4. Patients will be able to have pan retinal photocoagulation (PRP) to any areas of developing retinal ischaemia if demonstrated on FA and will also be able to have PRP if they develop any sign of anterior segment neovascularization on monthly ocular examination.

Retreatment Criteria for Months Seven to Forty Six.

1. There is a greater than 50 micron increase in central retinal thickness on spectral domain OCT compared to lowest previous measurement.
2. There are new or persistent cystic retinal changes or subretinal fluid on spectral domain OCT or persistent diffuse oedema greater or equal to 250 µm central foveal thickness on spectral domain OCT.
3. There is a loss of 5 or more ETDRS chart letters from the previous best measurement in conjunction with any increase in central foveal thickness on spectral domain OCT.

3.2. Study population size

This calculation has been performed for a comparison of the mean number of Lucentis injections required in the second year (i.e. a rate between the two treatment groups using Poisson regression). The software PASS has been used for all calculations. A power of 80%

and two sided alpha level of 0.05 have been assumed. It has been estimated for the control group i.e. Lucentis monotherapy, that a mean total number of 6 injections will be required in the second year. The expected mean number of injections in the combination group (laser/Lucentis) is expected to reduce to 4.3 giving a ratio of the combination group to the control group (Lucentis monotherapy) of 0.72. With power of approximately 80% and a two sided alpha of 0.05, 52 patients are required overall to complete the study. Allowing for an approximate 10% drop out rate, a total of 58 patients should be sufficient to enrol at baseline. This drop out rate is based on evidence to date from the CRUISE 12 month study and the PI's clinical experience.

Inclusion criteria

1. Foveal centre involved macular oedema secondary to CRVO less than nine months in duration.
2. Mean central foveal thickness greater or equal to 250 microns on spectral domain OCT*.
3. Adults greater or equal to 18 years.
4. BCVA 20/40 to 20/320 (73 to 24 letters on ETDRS chart).
5. Clear ocular media and adequate pupillary dilation.
6. IOP \leq 25mmHg.
7. Written informed consent.
8. No other significant ocular pathology.
9. Willing, committed and able to return for all clinic visits and complete all study related procedures.

* Patients who have had a previous CRVO that has spontaneously resolved will be enrolled provided there is no evidence of macular damage that would confuse visual acuity improvements.

Exclusion criteria

The following are criteria for exclusion from participation in the study:

1. Any previous treatment for central retinal vein occlusion (including laser, steroids, or anti-VEGFs).
2. Brisk afferent pupillary defect.
3. Evidence on examination of any diabetic retinopathy.
4. CVA or MI within 3months prior to day 0.
5. Women of childbearing potential not using the contraception method(s) specified in this study (specify), as well as women who are breastfeeding.
6. Known sensitivity to study drug(s) or class of study drug(s).
7. Use of any other investigational agent in the last 30 days.

8. Any other ocular condition in the study eye that would prevent improvement in visual acuity, e.g. macular ischaemia, underlying macular degeneration, epi-retinal membrane.
9. Neovascularisation of the iris, disc or retina.
10. Previous treatment with intravitreal corticosteroids, intravitreal anti-VEGF agents or macular grid laser in previous 3 months.
11. Aphakia or presence of anterior chamber lens in the study eye.
12. Significant media opacities such as cataract.
13. Previous pars plana vitrectomy.
14. History of retinal detachment or surgery for retinal detachment..
15. Any condition which would preclude a patient's ability to comply with the study requirements or to be available for the duration of the study.
16. Any active infection involving ocular adnexa including infectious conjunctivitis, keratitis, scleritis, endophthalmitis as well as idiopathic or autoimmune-associated uveitis in either eye.
17. Extra capsular extraction of cataract with phacoemulsification within three months preceding baseline, or a history of post-operative complications within the last 12 months preceding baseline in the study eye (uveitis, cyclitis etc).
18. Contra indication to pupil dilation in either eye.
19. Anticoagulation with warfarin.

3.3. Quality assurance

Standardised protocols will be used for the intraocular injections of Lucentis, laser treatment to create the chorioretinal anastomosis, refraction, fluorescein angiography, measurement of best corrected visual acuity and OCT.

The major quality assurance features for the study are:

- Standardised data collection forms and procedures.
- Standardised eligibility criteria.
- Prospective and treatment allocation
- Adherence to treatment protocol and follow-up programme
- Patient masked to treatment allocation.

3.4. Treatments

Investigational therapy and reference therapy

Lucentis 0.5 mg intravitreal injection combined with L-CRA compared to Lucentis alone as per the CRUISE trial.

Treatment assignment, blinding and randomisation

Patients will be randomised 1:1 into the two treatment groups.

Assigning study number and randomisation

Treatment allocation: After signing the informed consent form, each patient will be randomised to receive study treatment using a series of serially numbered, opaque envelopes containing an assignment to “Injection alone” or “Injection plus L-CRA”. Treatment assignments will be compiled using a list of computer generated pseudo-random numbers in permuted blocks of variable size. Patients will be randomized for treatment in one eye only.

Concomitant therapy

1. Sector or pan retinal laser for neovascularisation of either the retina or iris at the investigator’s discretion.
2. Treatment of neovascularization at the L-CRA site with either sectorial PRP or VEGF antibodies
3. Peripheral PRP for areas of peripheral capillary nonperfusion
4. Vitrectomy surgery for either epiretinal scarring from the L-CRA site causing macular traction or nonresolving vitreous haemorrhage which prevents a view of the retina for 4 weeks or more.

Interruption or discontinuation of treatment

Every patient has the right to discontinue study participation at any time, and every patient may be discontinued from the study for any reason beneficial to his/her wellbeing. All data generated up to the time of discontinuation from the study will be analysed and the reason(s) for discontinuation will be recorded.

Study drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant safety risk for that patient. The following adverse events require study drug discontinuation:

- Retinal tear or detachment.
- Vitreous hemorrhage that does not resolve by the next scheduled dosing day.
- Three consecutive missed doses of study drug.

- Pregnancy.

Treatment compliance

Lucentis treatment is administered via intravitreal injection by the investigator; therefore, those patients who receive injections as scheduled by the investigator will be considered to be compliant. Lucentis and all other medications/significant non-drug therapies administered after the start of study drug will also be recorded.

3.5. Visits and assessments

Visit schedule and assessments

Visit schedules will be as outlined in Table 1 with injection procedures performed at monthly intervals (± 3 days) in the first two years and bimonthly or once every four months in years 3 and 4.

Table 1. Schedule of study procedures.

Year 1														
Month (± 3 days)														
	Baseline	0	1	2	3	4	5	6	7	8	9	10	11	12
Ophthalmic Exam	x		x	x	x	x	x	x	x	x	x	x	x	x
Informed consent	x													
Randomisation + LCRA or sham		x												
Injection			x	x	x	x	x	x	(x)	(x)	(x)	(x)	(x)	(x)
Telephone Check			x	x	x	x	x	x	(x)	(x)	(x)	(x)	(x)	(x)
ETDRS visual acuity	x	x	x	x	x	x	x	x	x	x	x	x	x	x
OCT	x		x	x	x	x	x	x	x	x	x	x	x	x
FA & Colour Photos	x							x						x
Year 2														
Month (± 3 days)														
		13	14	15	16	17	18	19	20	21	22	23	24	
Ophthalmic Exam			x	x	x	x	x	x	x	x	x	x	x	
Injection			(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	
Telephone Check			(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	
ETDRS visual acuity			x	x	x	x	x	x	x	x	x	x	x	
OCT			x	x	x	x	x	x	x	x	x	x	x	
FA & Colour Photos							x						x	
Years 3 and 4.														
Month (± 7 days)														
		26*	28*	30*	32*	34*	36*	38*	40*	42*	44*	46*	48	
Ophthalmic Exam			x	x	x	x	x	x	x	x	x	x	x	
Injection			(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	
Telephone Check			(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	
ETDRS visual acuity			x	x	x	x	x	x	x	x	x	x	x	
OCT			x	x	x	x	x	x	x	x	x	x	x	
FA & Colour Photos													x	
OCTA + Additional OCT**														

*** = in years 3 and 4, the patient may miss a visit if the vision is stable and there is no macula oedema. A patient must be seen once every 4 months.**

**** - OCTA and additional OCT images will be performed once at any time point in years 3 and 4.**

(x) = injection only if required (as determined by V/A and OCT, see Section 3.1 Retreatment criteria for months seven to forty six).

(x) = telephone call only if injection occurred.

Baseline Assessment:

The following baseline examinations will be performed within 14 days prior to randomisation and L-CRA /sham. The Baseline and Month 0 visit can occur on the same day.

1. Informed consent.
2. Best corrected visual acuity using 4 metre ETDRS backlit lighthouse chart.
3. Ophthalmic examination including Tonometry, examination of the iris and Gonioscopy prior to dilation, dilated fundus examination.
4. OCT using Spectralis and appropriate software.
5. FA: this will be done using a 60 degree Canon or wide angle Optus camera and will comprise the area of involvement with the CRVO and will monitor the degree of capillary non-perfusion.
6. Colour photos using standard fields involving the posterior pole CRVO involvement.

Month 0 Assessments:

This assessment maybe performed on the same day as the baseline assessment if the patient is eligible for the study.

1. 1. BCVA , only done if Month 0 assessment \geq 7days from Baseline assessment.
2. Randomized to receive L-CRA or sham L-CRA treatment.

Month 1-Month 6 Assessments

1. Best corrected visual acuity using 4metre ETDRS backlit Lighthouse chart.
2. Ophthalmic examination including Tonometry, examination of the iris prior to dilation (Gonioscopy at Month 6), dilated fundus examination.
3. OCT using Spectralis OCT and appropriate software.
4. FA at the 6 Month visit, using a 60 degree Canon or wide angle Optus camera and will comprise the area of involvement with the CRVO and will monitor the degree of capillary non-perfusion.
5. Injection as outlined in the procedure in Section 7.
6. Telephone safety check to occur 3 days after each injection.

Month 7-Month 24 Assessments.

1. Best corrected visual acuity using 4metre ETDRS backlit Lighthouse Chart.
2. Ophthalmic examination including Tonometry, examination of the iris prior to dilation
Gonioscopy at Months 12, 18 and 24, dilated fundus examination.
3. OCT using Spectralis OCT and appropriate software.
4. FA at 12, 18 and 24 Month visits, this will be done with a 60 degree Canon or wide angle Optus camera and will comprise the area of involvement with the CRVO and will monitor the degree of capillary non-perfusion.
5. All patients will receive an injection (of their randomized treatment) if one or more of the following criteria are met:
 - There is a greater than 50 micron increase in central foveal thickness on spectral domain OCT compared to lowest previous measurement.
 - There are new or persistent cystic foveal changes or subretinal fluid on spectral domain OCT or persistent diffuse oedema greater or equal to 250µm in the central foveal thickness on spectral domain OCT.
 - There is a loss of 5 or more ETDRS chart letters from the previous best measurement in conjunction with any increase in central foveal I thickness on spectral domain OCT .
6. Telephone safety check to occur 3 days after each injection. The safety check (telephone call) is not required if the patient does not receive an injection.

Month 26- 46 Assessments.

1. Best corrected visual acuity using 4metre ETDRS backlit Lighthouse Chart.
2. Ophthalmic examination including Tonometry, examination of the iris prior to dilation, dilated fundus examination.
3. OCT using Spectralis OCT and appropriate software.
4. OCTA and additional OCT imaging can be performed at any visit in Years 3 and 4.
5. All patients will receive an injection (of their randomized treatment) if one or more of the following criteria are met:
 - There is a greater than 50 micron increase in central foveal thickness on spectral domain OCT compared to lowest previous measurement.
 - There are new or persistent cystic foveal changes or subretinal fluid on spectral domain OCT or persistent diffuse oedema greater or equal to 250µm in the central foveal thickness on spectral domain OCT.

- There is a loss of 5 or more ETDRS chart letters from the previous best measurement in conjunction with any increase in central foveal I thickness on spectral domain OCT .
6. Telephone safety check to occur 3 days after each injection. The safety check (telephone call) is not required if the patient does not receive an injection.
 7. If a visit is missed (visual acuity is stable and macula oedema is absent), then a phone call at the missed visit will take place to ensure that the patient's vision remains stable.

Month 48 Assessment.

1. Best corrected visual acuity using 4metre ETDRS backlit Lighthouse Chart.
2. Ophthalmic examination including Tonometry, examination of the iris and Gonioscopy prior to dilation, dilated fundus examination.
3. OCT using Spectralis OCT and appropriate software.
4. FA: this will be done using a 60 degree Canon or Optus camera and will comprise the area of involvement with the CRVO and will monitor the degree of capillary non-perfusion.
5. Colour photos using standard fields involving the posterior pole and area of CRVO will be taken.

Both eyes will be examined at the Baseline, 24 Month and Month 48 visits, for all other visits, only the study eye needs to be assessed.

Laboratory tests

No laboratory tests will be performed.

3.6. Efficacy assessment

Primary Efficacy Variable

The number of Lucentis injections required in each group in the second year.

Secondary Efficacy Variable

1. Change in baseline in best corrected visual acuity at Months 6, 12 and 24.
2. Absolute change from baseline in central foveal thickness, assessed by spectral domain OCT at Months 6, 12 and 24.
3. Progression of capillary nonperfusion as measured by wide angle fluorescein angiography at Months 12 and 24.

4. The number of Lucentis injections required in each group from Month 24 to Month 46.
5. Analysis of the retinal capillary vasculature in patients with CRVO.

3.7. Safety assessments

3.7.1. Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory tests or other means, will be collected and recorded on the Adverse Event Case Report Form and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the event is not considered to be treatment-related.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment. Clinical events occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, when they are recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. its duration (start and end dates),
2. the severity grade (mild, moderate, severe)
3. its relationship to the study drug or procedure (suspected / not suspected),
4. the action(s) taken.

3.7.2. Serious adverse events

Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety each serious adverse event must also be reported to Novartis within 24 hours of learning of its occurrence. A serious adverse event is defined in general as an untoward (unfavorable) event which:

1. is fatal or life-threatening,
2. required or prolonged hospitalization,
3. was significantly or permanently disabling or incapacitating,
4. constitutes a congenital anomaly or a birth defect,
5. may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

Events not considered to be serious adverse events are hospitalizations occurring under the following circumstances: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the criteria above); are part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

Reporting responsibility

The investigator is responsible for submission of Serious Adverse Events to both the TGA and Novartis within the required timelines. Each serious adverse event (or pregnancy) must be reported by the investigator to Novartis within 24 hours of learning of the occurrence, even if it is not felt to be treatment related. Follow-up information about a previously reported serious adverse event must also be reported to Novartis within 24 hours of receiving it. If the serious adverse event has not been previously documented (new occurrence) and it is thought to be related to study drug, the Medical Safety Expert of the Clinical Safety & Epidemiology Department may contact the investigator to obtain further information. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same drug that this serious adverse event has been reported.

Reporting procedures

The investigator must complete the Serious Adverse Event Report Form in English, assess the relationship to study treatment and send the completed form by fax (1800 650 493) within 24 hours to the local Novartis Drug Safety and Epidemiology Department. The original and the duplicate copies of the Serious Adverse Event Form, and the fax confirmation sheet must be kept with the case report forms at the study site. Follow-up information is sent to the same person to whom the original Serious Adverse Event Form was sent. A new Serious Adverse Event Form is completed, stating that this is a follow-up to the previously reported serious adverse event. The follow-up should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or discontinued study participation. The form and fax confirmation sheet must be retained.

3.7.3. Pregnancies

Any pregnancy that occurs during study participation should be reported using a Clinical Trial Pregnancy Form. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

4. Visual functions

4.1 Introduction

Since the major outcome of the trial will be measured by visual acuity the procedures for refraction and measurement of visual acuity should be followed carefully so that accurate reproducible and consistent measurements are obtained.

4.2 Procedures for Refraction and Vision Testing

Refraction and visual acuity measurements will be performed for all patients by a trained vision examiner. Another examiner should also be trained to serve as a back-up should the primary examiner be absent. The name of the vision examiner should be documented in the patient's source document at each visit.

4.2.1 Visual Acuity Testing

Best-corrected visual acuity is measured at all study visits using standard charts, lighting, and procedures. Best correction is determined by careful refraction at that visit according to the standard protocol for Refraction as described in the following section.

4.2.1.1 Visual Acuity Charts

Chart 1 is used for testing the visual acuity of the right eye; Chart 2 for testing the left eye; and Chart R for testing refraction only. Patients should not be allowed to see any of the charts before the examination.

4.2.1.2 Visual Acuity Lane and Visual Acuity Box

A distance of 4 metres is required between the patient's eyes and the visual acuity chart. With the box light off, not more than 15 foot-candles of light (161.4 Lux) should fall on the centre of the chart. To measure the amount of light, the room is set up for visual acuity testing, but with the box light off. The light meter is placed at the fourth line from the top of the chart, with its back against the chart and the reading is taken. If more than one lane is available for testing visual acuity, the visual acuity of an individual patient should be

measured in the same lane at each visit, if possible. If different lanes are used to test visual acuity, they must each meet the same standards.

Retroilluminated LOGMAR charts are used in this study. The illuminator box will be either wall-mounted or mounted on a stand manufactured.

The visual acuity light box is equipped with two General Electric Cool Daylight 20-watt fluorescent tubes and a ballast. Because the illumination of fluorescent tubes diminishes by 5 percent during the first 100 hours and by another 5 percent during the next 2000 hours, new tubes should be “burnt-in” by keeping them on for 4 days (96 hours) continuously, and should be replaced once a year.

A sticker should be placed on the back of the light box, indicating the date on which the present tubes were burnt-in and installed. A spare set of burned in bulbs should be available on site.

Each tube is partly covered by a fenestrated sleeve, which is open in the back. This serves as a buffer to reduce illumination. Each sleeve should be centered on the tube with the opening towards the back.

4.2.1.3 Best Corrected Visual Acuity Measures

- As a reminder, Charts 1, 2, and R are used for testing the right eye, left eye, and refraction, respectively. Patients should not see the charts until the test begins.
- The patient should be seated comfortably directly in front of the chart so that the eyes remain at the 4 metre distance. Testing always begins with the right eye. Occlude the patient’s left eye. A folded tissue lightly taped behind the trial frame serves as an effective occluder that allows eccentric fixation without inadvertent use of the covered eye. After testing the right eye, occlusion of the right eye should be done BEFORE Chart 2 is put up for testing the left eye.
- The lens correction from the subjective refraction should be in the trial frame worn by the patient.
- The patient is asked to read the letters slowly, approximately one letter per second. The patient should be told that only one chance is given to read each letter on the chart. If the patient is unsure about the identity of the letter, then the patient should be encouraged to guess. Remind the patient that there are only letters and no numbers on the chart.
- The patient should begin by reading the top line of the chart and continue reading every letter on each smaller line, from left to right on each line. The examiner circles every correct letter read and totals each line and the whole column (0 if no letters are correct) on the data collection form. Patient should continue until the last letter it is possible for them to read. When a patient reaches a level where he/she cannot guess, the examiner may stop the test provided that the patient has made errors on previous guesses, which is a clear indication that the best visual acuity has been obtained.

- When a patient cannot read at least 20 letters on the chart at 4.0 metres, the patient is moved closer to 1.0 meter from the chart. The spherical correction in the trial frame should be changed by adding +0.75 diopters to correct for the closer test distance. The patient may fixate eccentrically or turn or shake his/her head to improve visual acuity. If this is done, the examiner must ensure that the fellow eye remains occluded both centrally and peripherally and that the patient does not move forward in the chair.
- The examiner should not tell the patient if a letter was identified correctly. The patient may be encouraged by neutral comments, such as “good”, “next”, and “OK”.
- The examiner should not stand close to the chart during testing. Attention should be focused on the patient and the data collection form. If the patient has difficulty locating the next line to read, the examiner may go up to the chart and point to the next line to be read, but then must move away from the chart.
- When it is possible to measure the visual acuity of the eye at 4.0 metres (i.e. 20 or more letters read at 4.0 metres), the visual acuity score for that eye is recorded as the number of letters correct plus 30. The patient gets credit for the 30 1M letters even though they did not have to read them. Otherwise, the visual acuity score is the number of letters read correctly at 1.0 meter plus the number, if any, read at 4M. If no letters are read correctly at either 4.0 metres or 1 metre, then the visual acuity score is recorded as 0.

4.2.1.4 Testing for Count Fingers Vision, Hand Motion Vision and Light Perception/No Light Perception Vision

If the patient’s visual acuity is so poor that he/she cannot read any chart letters when tested at one meter then the patient’s ability to count fingers, detect hand motion, or have light perception should be evaluated.

Testing for Count Fingers Vision

In testing for count fingers vision, the examiner’s hand holding 1, 2, or 5 fingers is held steady at a distance of two feet directly in front of the eye being examined. The fellow eye is completely occluded with a patch on the face. A light should be shown directly on the hand from behind the patient. The examiner’s fingers should be presented in random order and repeated 5 times. Eccentric fixation, if present, should be encouraged. If the patient correctly identifies three of the five presentations, then count fingers vision is noted. If not, then the patient must be tested for hand motion vision.

Testing for Hand Motion Vision

The examiner’s hand with all fingers spread out should be extended two feet directly in front of the eye being examined. The fellow eye should be occluded with a patch on the patient’s face. A light should be shone directly on the hand from behind the patient. The examiner’s hand should be moved in an up-and-down direction (vertically) or in a side-to-side direction (horizontally) at a constant speed of approximately one back and forth presentation per second. The patient is instructed that the examiner’s hand will be presented and they will

have to respond to the question: “What am I doing with my hand?” This should be repeated five times. Three out of five correct responses indicate that hand motion vision is present. If the patient does not correctly identify three of five presentations, then you must test for light perception.

Testing for Light Perception/No Light Perception Vision

Light perception should be tested with an indirect ophthalmoscope in a darkened room. The indirect ophthalmoscope light should be in focus at 1 meter with the rheostat set at maximum voltage. From that distance the beam should be directed in and out of the eye at least four times, and the patient should be asked to respond when he or she sees the light. If the examiner is convinced that the patient perceives the light, vision should be recorded as “light perception”, if not, vision should be recorded as “no light perception”.

EXHIBIT 4.2.3

Refraction Protocol Summary							
Vision with Best Correction (Refraction Distance)	Sphere		Cylinder			Sphere Refinement	
	Power (a)	Increment	Axis (b)	Power (c)	Increment	Power (d)	Increment
20/20 - 20/80 (4 metres)	+1.50 -1.37	+1.50 -1.25	.50 JCC	.25 JCC	+1.25 -1.25	+1.25 -1.37	+1.25 -1.25
20/100 - 20/200 (4 metres)	+1.00 -1.00	+1.00 -1.00	.50 JCC	.50 JCC	+1.50 -1.50	+1.50 -1.50	+1.50 -1.50
<20/200 - 20/400 (1 metres)	+2.00 -2.00	+2.00 -2.00	1.00 JCC	1.00 JCC	+1.00 -1.00	+1.00 -1.00	+1.00 -1.00
<20/400 (1.0 metres)	+2.00 -2.00	+2.00 -2.00	No cylinder test			No refinement	

Sequence of Refraction: (a) - (d)

4.2.2. Refraction

Refraction should be conducted prior to visual acuity testing to obtain best-corrected vision.

4.2.2.1 Equipment

Refraction equipment required includes:

1. Retroilluminated Chart R from Ferris-Bailey LOGMAR distance visual acuity chart set¹
2. Trial lens frames
3. Trial lens set with plus or minus cylinder lenses
4. +0.37, + 0.50 and -0.37 spherical lenses
5. Jackson cross-cylinders of 0.25, 0.5, and 1.00 diopters
6. Pinhole occluder
7. Tissues.
8. A 1 and 2 meter rigid measuring stick

4.2.2.2 Beginning Approximate Refraction

At the Baseline visit, the patient's beginning refraction is determined by one of the following ways:

- a) If the patient does not require glasses for distance vision begin the patient with plano.
- b) If the patient requires glasses for distance viewing, the glasses should be measured using a lensometer, and these measurements are used for the beginning refraction.
- c) If the patient wears contact lenses, they should be removed and one should wait 30 minutes before performing autorefractometry to determine the beginning refraction.

Refractions are performed with plus cylinder power. Best correction will be recorded on a Subjective Refraction Record for each patient to be included in the source document. At each follow-up visit, the results of the protocol refraction from the previous visit are used as the beginning approximate refraction. If the previous refraction is not available for whatever reason, the procedure described immediately above should be used. Note that the distance prescription worn in glasses should be used only for the Baseline Visit.

The charts used for measuring distance visual acuity must NOT be used for refraction. Refraction for each eye should be performed at 4 metres unless the patient's visual acuity measured at 4 metres on the refraction chart (Chart R) is worse than 20/320 (6/36). If visual acuity is 6/320 (6/96) or worse, the eye is refracted at 1.0 meter. Whenever a patient cannot read any letters on the top line of Chart R at 1.0 meter at the beginning approximate refraction, the vision should be checked with a pinhole to see whether reduced vision is due, at least in part, to larger refractive error. If there is no improvement with the pinhole, then the eye is exempt from refraction.

Contact lenses should be removed at least 30 minutes before beginning the refraction.

Subjective refraction as described below should be performed for all patients. However, for uncorrected aphakic patients, a +10.00 diopter sphere should be added to the trial frame as the beginning approximate refraction.

4.2.2.3 Subjective Refraction

Subjective refraction allows one to determine the best correction for a patient to perform the visual acuity tests at specified distances. The “push plus” approach is used in this study. Add minus diopter spherical corrections only when the patient is able to read at least one more letter on a line or read at least one letter on a smaller line.

Procedure:

1. Measure and record the distance vision of each eye using Chart R while occluding the fellow eye. Patients should be encouraged to use eccentric fixation, or their side vision, when necessary.
2. Seat the patient at 4 metres or 1.0 meter from Chart R, depending upon the visual acuity determined at 4 metres. A rigid measuring device should be used to measure the distance from the patient to the chart at each visit. The distance is measured from the outer canthus to the center of the second letter (left eye) or fourth letter (right eye) of the third line of the chart.
3. Place and adjust the trial frame on the patient’s face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupils. Adjust the lens cells for the proper distance from the cornea.

4. Occlude the left eye by lightly patching with an eye pad or tissue and tape.
 - a) Place the spherical lens correction in the compartment closest to the eye.
 - b) The cylindrical lens correction, if present, is placed in the compartment in front of the spherical correction. Adjust the axis.

5. **Spherical Correction:** To determine the highest plus or least minus sphere, refract the right eye. The following refraction steps are recommended for visual acuities of 20/20 to 20/80 with the beginning approximate refraction. For visual acuities less than 20/80, refer to the refraction table for the appropriate sphere and cylinder powers and testing distance (See **Exhibit 8.2.3**) and follow a similar procedure using steps in power that are equal to the power of the lens being presented. *Note: Whenever visual acuity is improved to a higher range by improved correction, refinement should be performed with the smaller sphere and cylinder powers given for the better visual acuity.*
 - a) Hold a +0.50 sphere in front of the patient's right eye. The patient should be looking at the smallest legible line on the visual acuity chart. In these exact words, ask the patient, "Is this better, worse, or no change?"
 - b) If the patient responds better or no change, proceed to Step 5c. If the patient responds that the vision is worse or blurred, remove the +0.50 sphere from in front of the trial frame, go to Step 5d.
 - c) Remove the +0.50 sphere from in front of the trial frame and replace the spherical lens in the trial with a spherical lens that is one-half diopter more positive. Continue this procedure by returning to Step 5a and repeating this process until a +0.50 makes the vision worse.
 - d) Hold a -0.37 sphere in front of the patient's right eye. In these exact words, ask the patient, "Is this better, worse or no change?" If the patient replies "worse" or "no change", go to Step 5f. If the patient replies better, hold the -0.37 lens in front of the right eye again and ask whether the letters are easier to read or just smaller and darker. If the patient replies that it is actually "easier to read", go to Step 5e. If the patient says "smaller and darker" proceed to Step 5f.
 - e) If the patient responds that the vision is better (with the -0.37 lens in place), ask the patient to read the visual acuity chart. Whenever the visual acuity is improved, even by one letter, replace the spherical correction in the trial frame with a sphere, which is one-quarter diopter (0.25) less positive and repeat Step 5d. Whenever visual acuity is not improved, go to Step 5f.
 - f) Remove the -0.37 sphere from in front of the eye and hold a +0.50 sphere in front of the right eye. In these exact words, ask the patient, "Is this better, worse, or no change?". If the patient responds that vision is better or unchanged, then return to Step 5c. Otherwise, go to Step 6.

6. **Cylinder Axis:** To determine and refine the cylinder axis for PLUS cylinder, proceed as follows:

- a) Have the patient look at a line, which is either one or two lines larger than the smallest line the patient is able to read. Ask the patient to focus on a rounded letter such as “C”, “G”, or “O”. The patient should focus on this same letter throughout this procedure.
- b) If a cylinder is present in the beginning approximate refraction, then go to Step 6c. Otherwise, follow one of the options listed below to determine the appropriate cylindrical correction.

Option 1:

Place the +0.50 diopter cross-cylinder with the positive axis (white) first at 90°, then at 180°, then 45°, and 135°. If the patient says that vision is improved at any one of these axis positions, place a +0.50 cylindrical lens in the trial frame at the preferred axis and go to Step 6c. If none of the positions are preferred, then proceed to Step 8.

Option 2:

Place the +0.50 diopter cross-cylinder with the positive axis (white) first at 90°, then compare this to no cylinder; repeat this procedure for 180°, then 45°, and 135°. If the patient say that vision is improved at any one of the four axis positions, place a +0.50 cylindrical lens in the trial frame at the preferred axis. If the patient prefers no cylinder at all four axis positions, then go to Step 8.

- c) Place the +0.25 diopter cross-cylinder first with the positive axis 45° to the right of the cylinder axis, and second with the positive axis 45° to the left of the cylinder axis. Ask the patient, “Which is better, position one or two, or are they the same?” Also, tell the patient that both positions may blur vision. The patient must choose the least blurred position, either one or two. “Neither” is allowed only if both positions are equally blurred or equally good
- d) If “neither” position is better and this was the first test of axis position, move the axis of the cylinder in the trial frame 15° to the right or left and return to Step 6c. Otherwise, proceed to Step 6e.
- e) When one position is preferred over another, move the cylinder to the preferred positive axis position in the step sizes noted below and return to Step 6c. If no single position is better than another than go to Step 7.

CYLINDER REFINEMENT - AXIS STEP SIZES

Cylinder Power	Axis Step Sizes
<1.00D	15°
1.00 - <2.00D	10°
2.00 - <3.00D	5°
3.00 - <5.00D	3°
5.0 - <8.00D	2°

7. Cylinder Power: Cylinder power is refined by following the steps:

- a) Ask the patient to look at the smallest line that can be read on the visual acuity chart.
- b) Test the cylinder power by placing the 0.25 diopter cross-cylinder first with the positive axis and second with the negative axis coincident with the cylinder axis. Ask the patient,

- “Which is better, position one or position two or are they the same?” Do not give the patient the choice of neither.
- c) If the patient prefers the negative (red) axis coincident with the cylinder axis, the total power of the correcting plus cylinder is reduced by 0.25 diopter. Repeat the process until the patient cannot choose one of the cross cylinder positions over the other. If the patient indicates a change that would introduce negative cylinder power, remove all cylinder power and continue testing for positive cylinder power at an axis 90° away from the previous axis. Otherwise go to Step 7d.
 - d) If the patient prefers the positive (white) axis coincident with the cylinder axis, increase the power of the trial frame by 0.25 diopters and return to Step 7b. Otherwise proceed to Step 7e.
 - e) When the patient feels that both positions are equally bad or good, and the cylinder power in the trial frame has changed by more than 0.50 dioptres, the spherical equivalent should be maintained (For each 0.50 **plus** CX increase, add -0.25 to the sphere, for each 0.50 **minus** CX increase, add +0.25 to the sphere). then the cylinder axis should be refined again (see step 6c)
8. **Spherical Correction Refinement:** Recheck the power of the sphere by adding +0.37 and -0.37 spheres and changing the spherical power by 0.25 diopter increments of the appropriate sign until the patient cannot detect any improvement in vision.
 9. Record the lens corrections obtained by subjective refraction for the right eye on the examination form in the section for visual acuity measurements as the corrections obtained by protocol refraction for the right eye. If the corrective power was changed by more than 2 diopters from the starting refraction, confirm that the patient can read at least as well as the beginning approximate refraction. If not, then begin again at Step 1 and repeat the process.
 10. Repeat the entire process (Steps 1-9) for the left eye and record the result on the examination form.

5. Photography / Fluorescein Angiography

5.1. Introduction

The photographic documentation of eligibility and changes during follow-up are a vital part of this study.

The fundus camera for the study is the Canon 60 degree and the OPTUS super wide angle camera. FFAs and colour photographs will be performed digitally.

5.2. Fundus colour photographs

Standard fields involving the posterior pole, area of central retinal vein occlusion and the anastomosis will be taken at baseline, and the 6, 12, 18, 24 and 48 month visits.

5.3. Fluorescein angiography

Fluorescein injection: 5cc of 10% sodium fluorescein will be rapidly injected into the antecubal vein. Other injection sites may be substituted if necessary.

Standard angiogram will be presented as 4 UP (RF, <30sec, 60-90 sec, 5 min) at baseline, Month 6, Month 12, Month 18, Month 24 and Month 48 visits.

6. Optical Coherence Tomography

6.1. Introduction

Optical Coherence Tomography (OCT) is a diagnostic imaging technique using low-coherence interferometry to produce cross-sectional tomograms of the posterior segment eye structures. An 850 nm light source emits a probe beam of infrared light, which is split between the eye and a reference mirror at a known spatial location. Both beams are reflected back to a photo detector, the time of flight delay of light back scattered from different layers in the retina is determined, and thickness data are obtained. The OCT's internal computer acquires and processes the data to produce enhanced images by adjusting for movements of the eye, and fluctuations in intraocular pressure. Retinal thickness is determined using many individual A-scans along each of six B-Scans. A computer algorithm is used to determine the inner and outer retinal boundaries for each scan.

The Heidelberg Spectralis OCT will be used for this study and will be performed at all study visits.

6.2. Examination procedure

The eye(s) should be maximally dilated to help insure optimal quality scans.

Both the Macular Thickness and the Fast Macular Thickness acquisition protocol are to be used for this study.

The Macular Thickness protocol is used to acquire six high quality scans through the fovea for clinical purposes in addition to FFA, i.e. to determine if there is cystic macular oedema present involving the fovea. This information is needed to take decisions like the indication for re-treatment for example.

The Fast Macular Thickness Protocol is used to calculate the different thickness map parameters for statistical analysis of the outcome data. (Thickness maps can be calculated from the standard protocol as well, but fixation seems to be more stable with the fast protocol.)

6.3 Additional OCT images in years 3 and 4.

At the visit where the OCTA is performed, additional OCT images will be acquired. These are:

1. Retinal nerve fibre layer (RNFL) thickness will be measured around the optic nerve head using 16 automatically averaged B scans with 3-4 mm diameter.
2. High density macular scan
3. Enhanced depth imaging (EDI)-OCT will be used to determine subfoveal choroidal thickness.

6.4 Reading Centre

All copies of the Retinal Colour Images, FA and OCTs will be read and analysed by Prof. I McAllister.

7 Optical Coherence Tomography Angiography (OCTA)

7.1. Introduction

OCTA is a non-invasive imaging technique that generates volumetric data of the retinal and choroidal layers. OCTA provides a detailed view of the retinal vasculature and allows for the accurate delineation of microvascular abnormalities. It is used here to determine the nature and sequence of changes to the radial peripapillary capillaries and deep capillary networks. The microvascular changes at the sites of collateralization, optociliary shunts and chorioretinal venous bypass will also be investigated. These changes may provide predictors of visual acuity in CRVO.

7.2 Examination Procedure

Areas to be imaged in each eye are shown below in Figure 1. Both eyes of each participant will be imaged.

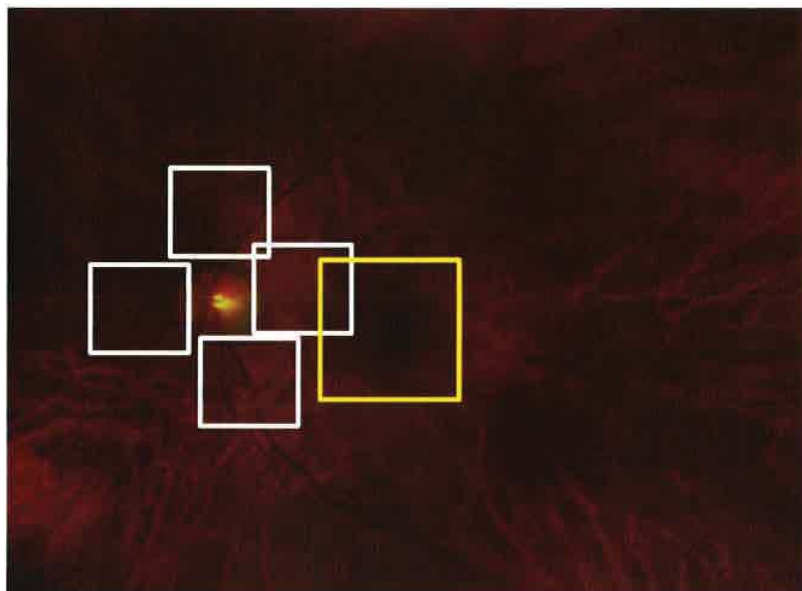


Figure 1. Areas to be imaged using OCTA.

3x3mm areas will be imaged. There are four areas around the optic nerve head as well as the central macula. The areas of optociliary shunt vessels, collateralization and venous bypass sites will also be selectively imaged.

8. Injection Procedures

The injections procedures for the L-CVBS study will be as outlined in the recent Royal Australian and New Zealand College guidelines for intraocular injection. Treatment injections will be given via a 30-gauge needle.

9. L-CRA Procedure

The L-CRA will be created using the purpose built Ellex laser with the same power settings as in CVBS study. The sham L-CRA procedure will use a power of 50mW with a spot size of 500u and duration of 0.1 sec. This will be directed into the far nasal periphery and the subject will experience a green flash similar to the standard laser. The power used will have no tissue effect.

10. Data management and Statistical Methods

The information required by the protocol will be entered into Case Report Forms (CRFs) developed by the Lions Eye Institute. The data will be summarised with respect to demographic and baseline characteristics and efficacy and safety observations. For all patients only one eye will be treated but for both eyes efficacy and safety parameters will be recorded.

An interim analysis will be take place after approximately 50% of the expected recruitment has occurred to evaluate the effect of the two treatment protocols on increase in visual acuity and reduction in OCT. The occurrence of adverse events will be used to assess safety and tolerability of the two procedures.

Independent sample t tests will be performed to assess the improvement of visual acuity or OCT due to Ranibizumab injections alone over Ranibizumab injections plus L-CRA. The hypotheses are to test

- (1) $H_{0,RI}: \mu_{VA,RI} \geq \mu_{VA,S}$ vs. $H_{1,RI}: \mu_{VA,RI} < \mu_{VA,S}$
- (2) $H_{0,RI}: \mu_{OCT,RI} \leq \mu_{OCT,S}$ vs. $H_{1,RI}: \mu_{OCT,RI} > \mu_{OCT,S}$

RI refers to Ranibizumab injections alone, S to Ranibizumab injections plus L-CRA, H_0 for null hypothesis and H_1 for alternative hypothesis.

The final analyses will be performed after 24 months when the expected recruitment will be completed. The analyses include

- (1) Patients demographic and baseline characteristics will be summarized for all subjects to describe the study population and evaluate treatment group comparability. Continuous variables (for example, age) will be summarized by descriptive statistics (c.g. mean, SD); and categorical variables will be summarized by frequency distribution (n, %). The medical history will be summarized by presenting for each treatment group.
- (2) The primary outcome will be the number of Lucentis injections between the two groups during the observational period from 12-23 months.

This has been done for a comparison of the mean number of injections required in the second year (i.e. a rate between the two groups using poisson regression). The PASS has been used for all calculations. A power of 80% and two sided alpha level of 0.05 have been assumed. There has been estimated for the control group i.e. Lucentis alone, a total number of six injections will be required in the second year. The expected ratio of the combination group to the control group will be 0.66 with the power to be around 80% and a two sided alpha of 0.05.

- (3) The secondary outcome regarding efficacy will be the percentage change in visual acuity and macular thickness measured by optical coherence tomography (OCT). The measurement at 24 month visit will be compared with baseline to evaluate the final improvement in addition to the investigation of trend based on each month's follow up. Statistical significant superiority can be seen for Ranibizumab injections (single or multiple injections) by using independent sample t tests described above in case of comparison between baseline and final visit. One way ANOVA will be used to

investigate the changes in means from baseline and Generalized Estimation Equation (GEE) models will be used to take time effect into account.

- (4) Logistic regression can be used for further explorative analysis of binary endpoints which will be considered during the data analysis stage and depending on the nature of the data.
- (5) The extension study will monitor the number of injections, stability of BCVA and macular thickness between the two treatment groups.
- (6) The assessment of safety will be based mainly on the frequency of adverse events, which includes all serious adverse events. Adverse events will be summarised by presenting for each treatment group the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate. Chi square test can be appropriate for this comparison.
- (7) In case a patient missed one or more applications of the study medication data of visits impacted by lack of compliance, will be replaced by the data of the first following visit displaying regular treatment.

11. References

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12. Signatures and Addresses

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